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Does A Single Dose Of Systemic Antibiotic Prevent Postoperative Inflammatory Complications After Lower Third Molar Surgery? A Randomized Controlled Trial.

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ABSTRACT

This study evaluates the effectiveness of a prophylactic single preoperative dose of amoxicillin in decreasing complications after lower third molar surgery. This study consisted of 400 patients indicated for third molar surgery who were randomly divided in two groups (200 patients per group). The first group of patients had never been diagnosed pericoronal inflammation while the second group consisted of patients with preoperative pericoronal inflammation. The both groups were divided in tested and control subgroups (100 patients per group). The tested subgroup received a prophylactic single dose of 2g amoxicillin one hour prior to the procedure. The second control subgroup received a placebo. Complications including swelling, alveolar osteitis, infection, limited mouth opening, pain, bleeding, and increased body temperature were evaluated postoperatively. The results of placebo subgroup within the first group were: a more statistically significant first degree swelling within 24 hours (P=0.048). The results of placebo subgroup within the second group were: pain intensity after seven days was significantly more intense (P=0.001) and the average duration of pain was significantly longer. Prophylactic dose of amoxicillin have a benefical effect on postoperative complications and can be recommended as a routine method in healthy patients with previous inflammation.

Keywords: third molar, oral surgical procedures, postoperative complications, antibiotic prophylaxis, placebo effect

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INTRODUCTION

Following a protocol in healthy patients, surgical procedures in the oral cavity have up to 3% of risk for development of infection [1]. The polymicrobial flora in the oral cavity, greatly represented by anaerobes, has a significant impact on the development of odontogenic infections, in particular postoperatively [2,3]. The third molar surgery (M3) comprises more than a half of all the procedures in oral surgery. Although these procedures are classified as so called 'clean' surgery, a prophylactic application of antibiotics is occasionally carried out in previously diagnosed pericoronitis or apical inflammation[1]. The operative procedure causes a damage to the surrounding bone and soft tissue, which can lead to an imbalance of microorganisms in the oral cavity and the development of postoperative complications. These complications are commonly related to the age, sex and general health of the patient, the grade of impaction and the duration of the surgical procedure, previous infections, condition of the tooth, hygiene of the oral cavity, other pathological changes in the immediate vicinity of the third molar, the surgeon's experience etc. [4-6]. Inflammatory reactions as pain, swelling, limitations in mouth opening, increased body temperature and general weakness of the patient are possible postoperative complications after M3 surgery. In some of the cases, postoperative hemorrhage or local purulent inflammation can appear, and may cause bacteremia which can then lead to a septic condition.

The pain following a surgical removal of the lower M3 has been the subject of investigation for decades, with the aim of improving the quality of life of patients in the postoperative period. The studies reviewed have not pointed to the effectiveness of the routine use of systemic antimicrobial drugs in preventing or reducing postoperative pain after the removal of impacted third molars in normal circumstances [7-8].

The aim of the presented study was to evaluate the effectiveness of a single prophylactic dose of amoxicillin in the prevention of local and systematic complications after lower third molar removal. The aim was also to propose clinical guidelines with respect to anantibiotic regimen.

METHODS

Study design and sample description

The study was registered via Clinical Trials (www.clinicaltrials.gov) with reference number ID of this study NCT03130933 and name of the trial register „Complications after lower third molar surgery".

This prospective study was performed at the Department of Oral Surgery of the Clinical Hospital Dubrava, Zagreb, Croatia, in the period from April 2010 to November 2016. All patients voluntarily agreed to participate in the study and signed informed written consents. The study was approved by the Ethics Committee of the School of Dental Medicine, Zagreb, Croatia (81-2009), according to the Declaration of Helsinki –Ethical principles for medical research involving human subjects. The identity of the subjects was protected in all phases of the study.

The exclusion criteria in this study were systematic diseases with increased risk for local infections, current smoking, pregnancy, lactation, usage of oral contraceptive drugs and any antibiotic coverage and sensitivity to penicillin.

The sample consisted of systematically healthy subjects between the ages of 18 to 40 (both genders) and having semi-impacted lower third molars indicated for surgical removal randomly divided into two main groups of patients. Unlike the patients from the second group, the first group of patients had never been diagnosed an inflammation in third molar area prior to the surgical procedure. The main test groups were further divided in two subgroups (control and tested): the tested subgroup (100 patients) received a prophylactic single dose of 2 grams of amoxicillin an hour prior to the procedure, while the second control subgroup (100 patients) received a placebo. No one knew what they have received, except researcher. The selection of the third molars for control and study subgroup was made according to the Pederson difficulty index [9]. According to this index (Table 1), the patients were classified into three groups: easy, moderate and difficult. The patients from this study who were classified into a difficult group were excluded from the study, due to a longer and more complicated surgical procedure with an expected prolonged recovery period and possible postoperative complications.

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Table 1: Pederson difficulty index of third molar removal (9).

Criteria	Value
Spatial relationship Mesioangular Horisontal / transverse Vertical Distoangular	 1 2 3 4
Depth of occlusal level of 3rd molar A (same as occlusal plane of 2nd molar) B (between occlusal plane and cervical line of 2nd molar C (below cervical line of 2nd molar)	 1 2 3
Space between the ramus and the distal part of the lower 2nd molar 1 (sufficient space) 2 (reduced space) 3 (no space)	 1 2 3
Difficulty index (A+B+C): Easy (Class I) Moderate (Class II) Difficult (Class III)	 3-4 5-6 7-10

Surgical procedure

Before the surgery all patients were informed in detail about the surgical procedure, its side effects, potential complications and possible risks. The surgical procedure was performed by the oral surgeons with more than 5 years of experience, in order not to influence the trauma level by the therapist's surgical experience. All surgical procedures were performed under local anesthesia (alveolar nerve block) with 2% lidocaine chloride, 1.8 ml, containing 1:80000 adrenaline (Belupo, Koprivnica, Croatia). Local anesthetic quantity in each procedure was two ampoules per patient. Before the procedure, every patient was asked to rinse the mouth with 0.2% chlorhexidine. The incision was of sufficient size in order to allow good visibility.

The full-thickness mucoperiosteal flap was raised using a buccal approach, an adequate osteotmy was done using micromotorhandpiece and bur, and third molar removal was finished using elevating instruments in the appropriate direction. The removal of bone dust, granulation tissue and broken tooth fragments was done in order to wound toileting. Gentle, sterile saline irrigation was done in the end. Primary closure of the surgical area was performed using 3-0 silk sutures (Silkam, B.Braun, Spain). No dressings or haemostatic agents were used after procedures. The average duration of the procedure was approximately 30 minutes per patient.The sutures were removed on the seventh postoperative day at the clinical follow-up. The patients received identical postoperative instructions and were advised to avoid smoking, exertion and to limit their activity for at least the rest of the day. They were asked to apply ice to their face for the first 24 hours and to keep their face elevated in order to reduce swelling. Rinsing and irrigating of the wound was not allowed for the first two days. They were instructed to brush their teeth, but to avoid brushing near the surgical wound for two days.

Post-operative evaluation

The patients were recalled for follow-ups on post-operative days one and seven. In all tested groups, the data was obtained by using identical questionnaires. The following symptoms were assessed: pain,

swelling, wound healing- alveolar osteitis (AO), infection at the surgical site (SSI) , maximum range of inter-incisal opening of mouth, increased body temperature and hemorrhage. A postoperative follow-up was always done by the same surgeon. Patients evaluated their postoperative pain with the grades ranging from 0-10 according to the visual analogue scale (VAS) The surgeon evaluated the type of post-extraction alveolus healing as normal healing, acute inflammation followed by infected alveolus or dry socket. The surgeon who assessed wound swelling did not know which group the patient was allocated to. The method of assessing the swelling was described in our previous study. The post-operative swelling was assessed on postoperative days one and seven, using a four-point scale as follows: 0=no swelling, 1=mild swelling, 2=moderate swelling, 3=severe swelling [10].

The maximum inter-incisal opening of the mouth was calculated from the mesioincisal angle of the ipsilateral mandibular central incisor to the mesioincisal angle of the ipsilateral mandibular central incisor using digital caliper (Caliper-Digital; Salvin Dental Specialties, Inc, Charlotte, NC).

Increased body temperature was measured by each patient at home during the postoperative period of seven days. The body temperature within 36.0ºC and 37.0ºC was evaluated as normal. The body temperature higher than 37.0 ºC was evaluated as increased. All temperatures were measured at the same time of the day, between 9:00 and 11:00 a.m.

Hemorrhage was observed by patients during the next seven days after the surgical procedure. It was classified as absent or present through the following days. Present hemorrhage was classified as light or intense.

The outcome variable was the presence or absence of an inflammatory complication after third molar surgery (SSI or AO). A diagnosis of SSI was identified by purulent discharge from the surgical site at any point postoperatively, fever, lymphadenopathy, pain and oedema warranting surgical intervention and/or systematic antibiotics). Alveolar osteitis was diagnosed in the cases of an empty alveolar socket, increased pain lasting for more than two days after surgery, and exposed alveolar bone tissue [11-13].

Statistical analysis

The statistical analysis was performed using Statistica 10.1 (StatSoft Inc., Tulsa, USA). The choice of the measure of central tendency and the measure ofvariability for age, sense of pain and duration of pain was determined by Kolmogorov-Smirnov's test. A comparative statistical analysis for age between the examined groups was determined by Kruskal-Wallis test, and Mann-Whitney test was used in a post-hocanalysis. A comparison of the duration and intensity of pain including all the examined parameters, i.e. swelling, hemorrhage and increased body temperature was done by using one-way ANOVA test. Tukey's test was used in the post-hoc analysis. The difference in the intensity of pain was evaluated by using the VAS and it was determined in the end of anesthesia, 24 hours after applying local anesthesia and seven days postoperatively.

For that purpose, Freedman's test and Wilcox's test were used in the post-hoc analysis. The prevalence of the patients with specific characteristics (gender) was shown by the frequencies and percentages and the significance of the difference in the frequency of prevalence between the groups and were tested by chi-square test. The post-hoc analysis was carried out by t-test of the difference in proportions. The level of statistical significance was set at a P value less than or equal to 0.05.

RESULTS

There were significantly more females in relation to the total number of males (54.3% vs. 45.7%; p=0.015). The results of the statistical analysis showed that in the group without previous inflammation, the two subgroups did not differ significantly (p=0.817), as well as in the group with previous inflammation (p=0.439), regarding age of patients. No significant difference between the subgroups within the first tested group (without inflammation) was determined in the stage of limited mouth opening and hemorrhage (p>0.05). Statistically significant differences were determined for the degree of swelling and increased body temperature (p<0.05) (Table 2). A significantly greater number of subjects treated with placebo had increased body temperature (p=0.42, p=0.012). When statistical significance was determined by chi-square, a post-hoc analysis was necessary in order to determine the stage of swelling for which the differences were

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significant, as well as t-test for proportion. For stage 1 swelling, determined within 24 hours and seven days after the procedure, there was a significantly greater number of subjects in the subgroup with placebo compared to the number of subjects who received antibiotic (p=0.048, p=0.001) (Table 2). A statistically significant difference for hemorrhage between the subgroups within the second tested group (with inflammation) was determined (p<0.001) (Table 3). A significantly greater number of subjects in the placebo group had a marked hemorrhage in the first postoperative day, compared with the number of subjects in the subgroup with inflammation who received an antibiotic (25% vs. 3%, P<0.001). The same significance for this category was also recorded after 24 hours, although with different individual values. No statistically significant differences were determined for other factors (Table 3).

Table 2: Distribution of subjects according to the stage of swelling, inter-incisal mouth opening, bleeding and increased body temperature within 24 hours and 7 days after the procedure / Group without previous inflammation (the first group).

Factor	Group without inflammation/N within 24 hours of the procedure		Statistics	Factor	Group without inflammation /N 7 days after the procedure		Statistics
	Antibiotic (N=100)	Placebo (N=100)			Antibiotic (N=100)	Placebo (N=100)	
Swelling							
Without	2	1	χ^2=7,91 P=0,048*	Without	55	29	χ^2=17,02 P<0,001*
1st degree	34	47		1st degree	45	66	
2nd degree	52	49		2nd degree	0	5	
3rd degree	12	3		3rd degree	0	0	
Limited mouth opening							
Without	5	7	χ^2=1,82 P=0,610	Without	54	60	χ^2=1,51 P=0,470
1st degree	43	39		1st degree	43	39	
2nd degree	50	49		2nd degree	3	1	
3rd degree	2	5		3rd degree	0	0	
Hemorrhage							
Absent	63	64	χ^2=5,54 P=0,063	Absent	69	66	χ^2=17,88 P<0,001*
Light	37	31		Light	30	17	
Intense	0	5		Intense	1	17	
Increased body temperature				Increased body temperature , Number of days			
Absent	94	84	χ^2=4,14 P=0,042*	Absent	99	84	χ^2=16,67 P=0,012*
Present	6	16		1day	0	3	
				2 days	1	8	
				3 days	0	3	
				4 days	0	1	
				5 days	0	1	

*statistical significance is present

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Table 3: Distribution of subjects according to the grade of swelling, inter-incisal mouth opening, hemorrhage and increased temperature within 24 hours and 7 days after the procedure / Group with previous inflammation (the second group).

Factor	Group with previous inflammation/N within 24 hours of the procedure		Statistics	Factor	Group with previous inflammation /N 7 days after the procedure		Statistics
	Antibiotic (N=100)	Placebo (N=100)			Antibiotic (N=100)	Placebo (N=100)	
Swelling							
Without	0	2	χ^2=3,50 P=0,320	Without	33	38	χ^2=3,38 P=0,184
1st degree	24	31		1st degree	64	62	
2nd degree	59	53		2nd degree	3	0	
3rd degree	17	14		3rd degree	0	0	
Limited mouth opening							
Without	4	9	χ^2=3,90 P=0,273	Without	53	58	χ^2=1,63 P=0,442
1st degree	30	22		1st degree	47	41	
2nd degree	54	60		2nd degree	0	1	
3rd degree	12	9		3rd degree	0	0	
Hemorrhage within 24 hours				Hemorrhage after 24 hours			
Absent	58	40	χ^2=14,10 P<0,001*	Absent	88	64	χ^2=14,50 P<0,001*
Light	32	57		1 day	3	25	
Intense	10	3		2 days	6	9	
				3 days	3	0	
Increased body temperature				Increased body temperature , Number of days			
Absent	87	80	χ^2=1,31 P=0,253	Absent	87	81	χ^2=5,76 P=0,335
Present	13	20		1day	1	4	
				2 days	4	9	
				3 days	7	4	
				4 days	1	1	
				5 days	0	1	

*statistical significance is present

There were no statistically significant differences between the incidence of AO and SSI in tested groups (p=0.156, p=0.668).

With regard to pain, no statistically significant difference in pain intensity was determined between the two subgroups in the group with no inflammation (Table 4).

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Table 4: Distribution of subjects according to pain after the effect of the anesthesia ceased, duration and intensity of pain after 24 hours and 7 days after surgery.

Factor	Pain intensity VAS / $\bar{x} \pm$ SD Group without inflammation		Statistics	Factor	Pain intensity VAS / $\bar{x} \pm$ SD Inflammation group		Statistics
	Antibiotic (N=100)	Placebo (N=100)			Antibiotic (N=100)	Placebo (N=100)	
Pain after the effect of the anesthesia ceased /VAS (0–10)				Pain after the effect of the anesthesia ceased /VAS (0–10)			
Median (10-90) percentile	5 (3–8)	6 (3–7)	0,167	Median (10-90) percentile	5(3–8)	6 (3–8)	0,520
$\bar{x} \pm$ SD	5,4 ± 1,8	6,5± 9,7	0,265	$\bar{x} \pm$ SD	5,6± 2,1	5,7 ± 2,1	0,587
Pain duration / hours				Pain duration / hours			
Median (10-90) percentile	24(12-24)	24(12-24)	0,766	Median (10-90) percentile	24(4,5-24)	24(18-24)	0,631
$\bar{x} \pm$ SD	21,2 ± 5,9	21,5 ± 5,9	0,736	$\bar{x} \pm$ SD	21,3± 7,0	22,0±6,1	0,542
Pain intensity after 24 hours /VAS (0-10)				Pain intensity after 24 hours /VAS (0-10)			
Median (10-90) percentile	4(2-6)	4(2-6)	0,387	Median (10-90) percentile	4 (1–7)	5 (2–7)	0,261
$\bar{x} \pm$ SD	3,9 ± 1,5	4,1± 1,9	0,476	$\bar{x} \pm$ SD	4,3± 1,9	4,6± 2,0	0,191
Pain duration /days				Pain duration /days			
Median (10-90) percentile	4(2-7)	4(2-7)	0,070	Median (10-90) percentile	4 (2–7)	7 (2–7)	<0,001*
$\bar{x} \pm$ SD	4,3 ± 1,5	4,0± 1,6	0,199	$\bar{x} \pm$ SD	4,2± 1,7	5,3± 2,2	<0,001*
Pain after 7 days /VAS (0-10)				Pain after 7 days /VAS (0-10)			
Median (10-90) percentile	0 (0–2)	0 (0–2)	0,752	Median (10-90) percentile	0 (0–4)	1 (0–3)	0,001*
$\bar{x} \pm$ SD	0,5 ± 1,1	0,4± 1,0	0,458	$\bar{x} \pm$ SD	1,0 ± 1,9	1,3±1,4	0,221

*statistical significance is present

In the group with previous inflammation, the subjects who received antibiotic showed statistically significant less pain expressed on the VAS scale, compared to the subjects who received a placebo with grade 2

swelling (p=0.013), grade 3 swelling (p=0.049) and with hemorrhage within 24 hours (p=0.003).

In the group with previous inflammation, no significant differences were determined for pain intensity after 24 hours between the subjects who received antibiotic compared to the subjects who received a placebo (both p>0.05), although after seven days the pain intensity experienced by the subjects with a placebo was statistically significantly greater compared to the subjects who received antibiotics (p=0.001). A significant difference was also determined for the duration of pain. The average duration of pain in the subjects with inflammation who received a placebo was seven days, while in the subjects who received antibiotic it was four days. Pain in the group with placebo lasted significantly longer (p<0.001).

DISCUSSION

The objective of this study was to determine whether the use of a single preoperative prophylactic dose of antibiotic, when compared to placebo, decreased the frequency of postoperative complications. Additionally, we tried to determine whether the previous inflammation associated with impacted M3 had an impact on postoperative complications. Reports concerning the type, dosage, administration or duration of antibiotics have been very heterogeneous and there is no consensus regarding the use of antibiotics in preventing postoperative complications in M3 surgery [14-21]. This topic remains controversial, because unnecessary application of antibiotics could promote bacterial resistance or some kind of adverse reaction, which is commonly reported in the literature [22-23]. However, a single prophylactic dose of antibiotics has never resulted in the development of resistance [24].

Postoperative risk factors include increasing age (older than 24 years), female gender, smoking, surgical trauma, length of surgery (longer than 30 minutes), level of impaction and surgeon's experience [25-27]. To standardize postoperative recovery, all procedures in the presented study were done by the same oral surgeon, Class 3 third molars according to Pederson difficulty index were excluded and all patients were healthy.

The results of statistical analysis of the age of patients showed that there was no statistical significance in groups. In the whole study group there were significantly more females in relation to the total number of males (54.3% vs. 45.7%; p=0.515). In similar studies there were also significantly more women than men. Blondeau and Daniel [28], in a sample of 327 patients had 58% female and 42% male patients, and in a sample of 366 patients, presented by Waite and Cherai [29], the difference was even greater: 61% ofwomen compared to 39% men. Blondeau and Daniel [28] showed that the rate of postoperative complications and the risks of permanent sequelae increase with age. They recommend that, once a decision has been made to extract an impacted mandibular third molar, the surgery should be carried out as soon as possible and well before the age of 24 years, especially for women.

Postoperative pain after surgical removal of the third molar occurs after the effect of the anesthesia ceases and pain intensity increases up to a maximum after 6-8 hours. If untreated, the pain on average lasts for 24 hours, after which it gradually decreases. The average duration of pain in the present study was significantly longer in the subjects who received a placebo (seven days), compared to antibiotic subgroup (four days) in the inflammation group. How could a single dose of amoxicillin reduce the intensity of pain and how can this mechanism be explained? Is it possible that in the subjects who reacted more intensely, apart from reactive inflammation and additional factors, there was the additional effect of microorganisms which increased the reaction of tissue, while in the group with prophylactic dose of antibiotic these factors were reduced? Some answers can be found in the data showing that there were statistically significantly more subjects with increased body temperature during seven postoperative days (p=0.012) in the subgroup of the same tested group who had received a placebo before the procedure. Similar results were found for pain, swelling and postoperative hemorrhage in the placebo subgroup with previous inflammation. If we compare the results of a study by Pavić [30] who applied a prophylactic dose of 500 mg amoxicillin and obtained a negative response with regard to its efficacy on postoperative complications, then the question arises whether the prophylactic dose of 2 g of amoxicillin applied in the present study was responsible for the partially positive results. Can surgical procedures, in which impacted M3 are removed, be classified as clean contaminated procedures, or are they clean procedures with a minor risk of postoperative infection? Classification of the sample into two examined groups and the different results of the study in these groups could provide the answer to this question. Surgical procedures of all M3 which had previously caused episodes

of pericoronal inflammation or periradicular lesions can be classified in the group of clean contaminated procedures and can therefore also contribute to the duration of the surgical procedure and the extent of the removed tissue. With regard to the difficulty in mouth opening, this commonly follows the two previously mentioned factors and is associated with them. Greater swelling and intensity of pain can be associated with more expressed difficulty in mouth opening. In our study, grade 1 difficulty of mouth opening was more marked in the subgroups without previous inflammation, while grade 2 and 3 difficulty mouth opening were more intense in the subgroups with previous inflammation, although in relation to other parameters no statistically significant differences which could be emphasized were found. A similar result for the incidence of difficulty in mouth opening after a prophylactic dose of 500 mg amoxicillin was also obtained in a study which does not recommend a routine usage of antibiotics before lower M3 surgery [30], but suggests that a combination of medical therapy with methylprednisol and ibuprofen proves to be a statistically significant effective treatment [31].

In the case of the development of local complications, the pain may last for several days, and a clinical examination of the wound and surroundings indicates the development of local inflammation. Many publications are focused on the correlation between prophylactic application of antibiotics and the incidence of the most common postoperative complications of SSI and AO following M3 surgery. The results of some studies [24,32,33] showed that a single preoperative dose of amoxicillin significantly decreased the incidence of SSI and AO. In this study, the overall rate of AO was 4.25 % and the rate of SSI was 1.75%, which is consistent with other publications [34-36]. In our study a prophylactic single dose of antibiotics did not have a statistically significant effect on postoperative infections in the inflammation group which is in agreement with previous study [37]. Previous studieswith preoperative and postoperative administration of amoxicilin, found statistically significant lesser occurrence of pain, infection of the wound, temperature, dysphagia and other side-effects in the groups who received amoxicillin before and after lower M3 surgery in relation to the group who received a placebo [38-40]. It was also observed that antimicrobial efficacy was more expressed in the group who received therapy postoperatively than in those who received a prophylactic therapy[38].

CONCLUSION

According to the results of the study, a single preoperative dose of amoxicillin have a statistically significant effect on certain postoperative complications in M3 surgery and it is recommended as routine method when M3 are removed in healthy patients with episodes of previous pericoronal inflammation. Significant difference was determined for the duration of pain, bleeding and body temperature.

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REFERENCES

[1] Hupp JR, Ellis III E, Tucker MR. Contemporary Oral and Maxillofacial Surgery. St Louis, Mosby Elsevier; 2008.
[2] Krmpotić M, Macan D, Škrlin J, Perić B. A Microbiological Study of Periapical Lesions in Single Rooted Teeth with Open and Closed Root Canal. Acta Stomatol Croat 2002; 36: 369-374.
[3] Bahl R, Sandhu S, Singh K, Sahai N, Gupta M. Odontogenic infections: Microbiology and management. Contemp Clin Dent 2014; 5: 307-311.
[4] Chuang SK, Perrott DH, Susarla SM, Dodson TB. Risk factors for inflammatory complications following third molar surgery in adults. J Oral Maxillofac Surg 2008; 66: 2213-2218.
[5] Baqain ZH, Karaky AA, Sawair F, Khraisat A, Duaibis R, Rajab LD. Frequency estimates and risk factors for postoperative morbidity after third molar removal: a prospective cohort study. J Oral Maxillofac Surg 2008; 66: 2276-2283.
[6] Chuang SK, Perrott DH, Susarla SM, Dodson TB. Age as a risk factor for third molar surgery complications. J Oral Maxillofac Surg 2007; 65: 1685-1692.
[7] Artegoitia I, Barbier L, Santamaría J, Santamaría G, Ramos E. Efficacy of amoxicillin and amoxicillin/clavulanic acid in the prevention of infection and dry socket after third molar surgery. A

systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal. 2016; 21: e494-504.
[8] Seymour RA, Walton JG. Pain control after third molar surgery. Int J Oral Surg 1984; 13: 457-485.
[9] Pederson GW. Oral surgery. Philadelphia,Saunders, 1988.
[10] Batinjan G, Zore Z, Čelebić A, Papić M, Gabrić Pandurić D, Filipović Zore I. Thermographic monitoring of wound healing and oral health-related quality of life in patients treated with laser (Apdt) after impacted mandibular third molar removal. Int J Oral Maxillofac Surg 2014; 43: 1503-1508.
[11] Dodson TD. HIV status and the risk of post-extraction complications. J Dent Res 1997; 76: 1644-1652.
[12] Dodson TB. Prediction of post extraction complications in HIV positive patients. Oral Surg Oral Med Oral Pathol 1997; 84: 474-479.
[13] Halpern LR, Dodson TB. Does prophylactic administration of systemic antibiotics prevent postoperative inflammatoray complications after third molar surgery? J Oral Maxillofac Surg 2007; 65: 177-185.
[14] Falconer DT, Roberts EE. Report of an audit into third molar exodontia. Br J Oral Maxillofac Surg 1992; 30: 183-185.
[15] Crincoli V, Di Comite M, Di Bisceglie MB. Which route of antibiotic administration should be used for third molar surgery? A split-mouth study to compare intramuscular and oral intake. Clin Ter 2014; 165: e12-16.
[16] Lockhart PB, Brennan MT, Kent ML, Norton HJ, Weinrib DA. Impact of amoxicillin prophylaxis on the incidence, nature and duration of bacteremia in children after intubation and dental procedures. Circulation 2004; 109: 2878-2884.
[17] Hall G, Nord CE, Heimdahl A. Elimination of bacteriemia after dental extraction: comparison of erythromycin and clindamycin for prophylaxis of infective endocarditis. J Antimicrom Chemoter 1996; 37: 783-795.
[18] Yoshi T, Hamamoto Y, Muraoka S, Furudoi S, Komori T. Differences in postoperative morbidity rates, including infection and dry socket, and differences in healing process after mandibular third molar surgery in patients receiving 1-day or 3-day prophylaxis with lenampicillin. J Infect Chemoter 2002; 8: 87-93.
[19] Ataoğlu H,Oz GY, Candirli C, Kiziloğlu D. Routine antibiotic prophylaxis is not necessary during opeartions to remove third molars. J Oral Maxillofac Surg 2008;46:133-5.
[20] EspositoS, Novelli A, Lalla F. Antibiotic prophylaxis in surgery: news and controversies. Infez Med 2002; 10: 131-144.
[21] Lee JY, Do HS , Lim JH, Jang HS, Rim JS, Kwon JJ, Lee ZS. Correlation of antibiotic prophylaxis and difficulty of extraction with postoperative inflammatory complications in the lower third molar surgery. Br J Oral Maxillofac Surg 2014; 52: 54-57.
[22] Alanis A, Weinstein AJ. Adverse reactions associated with the use of oral penicillins and cephalosporins. Med Clin North Am 1983; 67: 113-129.
[23] Hawkey PM, Patel BC, Trees AJ. UK antimicrobial resistence strategy must be set in a wider contex. BMJ 2013; 346: f2999.
[24] Marcussen KB, Laulund AS, Jorgensen HL, Pinbolt EM. A systematic review on effect of single-dose preoperative antibiotics at surgicel osteotomy extraction of lower third molars. J Oral Maxillofac Surg 2016; 74: 693-703.
[25] Conrad SM, Blakey GH, Shugars DA. Patients perception of recovery after third molar surgery. J Oral Maxillofac Surg 1999; 57: 1288-1294.
[26] Phillips C, White RP Jr, Shugars DA. Risk factors associated with prolonged recovery amd delayed healing after third molar surgery. J Oral Maxillofac Surg 2003; 61: 1436-1448.
[27] Phillips C, Gelesko S, Proffitt WR. Recovery after third molar surgery: The effects of age and sex. Am J Orthodont Dentoca Orthop 2010; 138: 700.e1-8.
[28] Blondeau F, Daniel NG. Extraction of impacted mandibular third molars: postoperative complications and their risk factors. J Can Dent Assoc 2007; 73: 325.
[29] Waite PD, Cherala C. Surgical outcomes for suture-less surgery in 366 impacted third molar patients. J Oral Maxillofac Surg 2007; 64: 669-673
[30] Pavić M. The influence of medical therapy on the reduction of swelling, pain and trismus after alveolectomy of the lower wisdom tooth. [Master's Thesis]. [Zagreb]:University of Zagreb School of Dental Medicine ; 2000.
[31] Mihelčić I. Antibiotic prophylaxis in alveolectomy of the lower wisdom tooth[Master's Thesis]. [Zagreb]: University of Zagreb School of Dental Medicine; 2012.
[32] Ren YE, Malmstrom HS. Effectiveness of antibiotic prophylaxis in third molar surgery: A meta-anaysis of randomized controlled clinical trials. J Oral Maxillofac Surg 2007; 65: 1909-1921.

[33] Lodl G, Figini I, Sardella A. Antibiotics to prevent complications following tooth extractions. Cochrane Database Syst Rev 2012; 11: CD003811.
[34] Bortoluzzi MC, Capella DL, Barbieri T. A single dose of amoxicillin and dexamethasone for prevention of postoperative complications in third molar surgery: A randomized, double-blind, placebo controlled clinical trial. J Clin Med Res 2013; 5: 26-33.
[35] Pasupathy S, Alexander M. Antibiotic prophylaxis in third molar surgery. J Craniofac Surg 2011; 22: 551-553.
[36] Monaco G, Tavernese L, Agostini R, Marchetti C. Evaulation of antibiotic prophylaxis in reducing postoperative infection after mandibular third molar extraction in young patients. J Oral Maxillofac Surg 2009; 67: 1467-1472.
[37] Isiordia-Espinoza M.A, Aragon-Martinez O.H, Martinez-Morales J.F, Zapata-Morales JR. Risk of wound infection and safety profile of amoxicillin in haelthy patients which required third molar surgery: a systematic review and meta-analysis. Br J Oral Maxillofac Surg 2015; 53: 796-804
[38] López-Cedrún JL, Pijoan JI, Fernández S, Santamaria J, Hernandez G. Efficacy of amoxicillin treatment in preventing postoperative complications in patients undergoing third molar surgery: a prospective, randomized, double-blind controlled study. J Oral Maxillofac Surg 2011; 69: e5-14.
[39] Conaty S, Hoang H, Kirshen D, Kwong C, Schroeder E, Stromme A. Pre and post-operative antibiotic prophylaxis in the prevention of complications following third molars surgery. http://docplayer.net/29390208-Pre-and-post-operative-antibiotic-prophylaxis-in-the-prevention-of-complications-following-third-molar-surgery.html#show_full_text
[40] Ong CKS, Seymour RA. Pathogenesis of postoperative oral surgical pain. Anesth Prog 2003; 50: 5-17.